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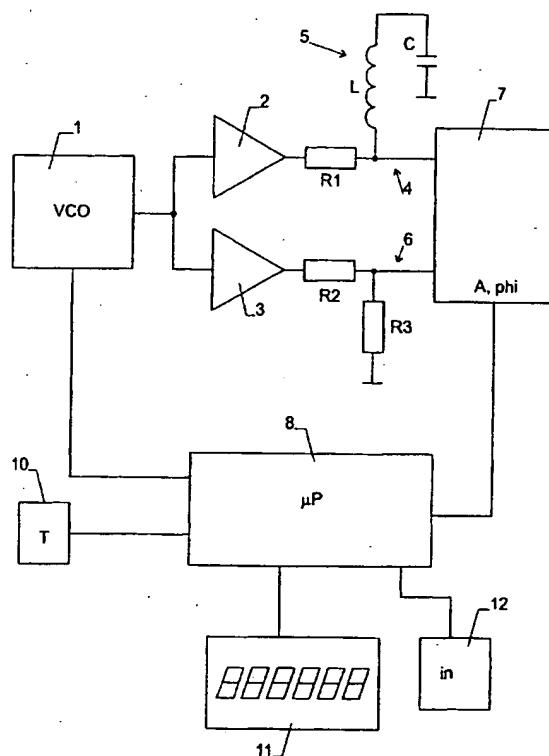
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(54) Title: METHOD AND DEVICE FOR DETERMINING THE CONCENTRATION OF A SUBSTANCE IN BODY LIQUID



WO 02/069791 A1



(57) Abstract: For measuring the concentration of a substance in body fluid, such as the glucose level in blood or tissue, a strip electrode (18) and a ring electrode (19) are arranged at the specimen. The ring electrode (19) is in direct electrical contact with the specimen while the strip electrode (18) is electrically insulated therefrom. The strip electrode (18) is arranged parallel to an arm or a leg for obtaining a large interaction length. The electrodes (18, 19) form a capacitor in a resonant circuit. A modulated voltage in the MHz range close to or at the resonance frequency is applied to the electrodes and the response of the body fluid is measured. This design allows a measurement of high accuracy.

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For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

Method and device for determining the concentration of a substance in body liquid

5 Technical Field

The invention relates to a method and a device for determining the concentration of a substance in an in-vitro or in-vivo specimen containing body liquid
10 according to the preamble of the independent claims.

Background Art

Radio wave spectroscopy has been known to
15 provide promising potential in the in-vitro and in-vivo determination of the concentration of glucose and other substances in body fluids. In particular, this technology is of substantial interest for the determination of glucose concentration in blood and/or inter- or intracellular liquid. A device for measuring blood level glucose is disclosed in US 5 792 668, where two electrodes are brought into direct contact with the human body and the impedance is measured between them.

Despite its potential, the technology has not
25 yet been used in commercial devices, which is attributed to the limited accuracy of the presently known solutions.

Disclosure of the Invention

30

Hence, it is the goal of the invention to provide a method and device that allow to increase the reliability of this type of measurement.

This goal is reached by the independent
35 claims.

In a first aspect of the invention, the first electrode is electrically insulated from the specimen.

Hence, the measured parameter does not depend on the surface conditions of the specimen. Rather, the signal is capacitively coupled to the specimen and the measured parameter depends therefore primarily on the conditions 5 within the specimen. The parameter measured in this way can then be converted to the desired concentration, e.g. by using calibration data.

Preferably, at least two electrodes are provided, wherein the modulated voltage is applied between 10 them. By using two electrodes, a defined field can be established within the specimen. For best signals, it has been found advantageous to place the second electrode in electric contact with the specimen.

The measured parameter preferably depends on 15 the electrical impedance at the electrode(s). It has been found that the concentration of various substances, in particular glucose, affects the real or imaginary part of this impedance because it changes the loss and/or dielectric constant of body fluid.

20 Preferably, the electrode forms part of a resonant circuit, which is operated at or close to its resonance frequency. Under such conditions, a change of the dielectric or loss properties of the specimen leads to substantial shifts in the parameters of the resonant 25 circuit and can therefore be measured with high sensitivity.

A further aspect of the invention is directed 30 to a device particularly suited for in-vivo measurements of the human body. This device comprises an elongate electrode having a width much smaller than its length. A holder is provided to mount the electrode to an arm or a leg with the longitudinal axis of the electrode extending parallel thereto. In this way, a large interaction space 35 is established, which allows to measure the desired concentration with a higher level of accuracy.

The method and device of the present invention has been found to be especially suited for measuring the glucose concentration in body fluid.

Brief Description of the Drawings

The invention will be better understood and objects other than those set forth above will become apparent when consideration is given to the following detailed description thereof. Such description makes reference to the annexed drawings, wherein:

Fig. 1 is a block circuit diagram of a preferred device for carrying out the invention,

Fig. 2 is a view onto a possible embodiment of the device,

Fig. 3 is a section along line III-III of Fig. 2,

Fig. 4 is the device of Fig. 3 with a wristband,

Fig. 5 shows the behavior of the relative amplitude A as a function of frequency,

Fig. 6 is a second embodiment of the circuit,

Fig. 7 is an alternative electrode geometry,

Fig. 8 shows measurements at varying glucose concentrations (mmol/liter) in physiologic solution and

Fig. 9 a third embodiment of the circuit.

Modes for Carrying Out the Invention

Fig. 1 shows a block circuit diagram of a preferred device for carrying out the invention. It comprises a voltage controlled oscillator (VCO) 1 as a signal source for generating a sine wave signal. This signal is fed to two amplifiers 2, 3. The output of first amplifier 2 is connected via a resistor R1 to a first signal

path 4. A resonant circuit 5 comprising an inductance L and a capacitor C in series is connected between first signal path 4 and ground. The output of second amplifier 3 is connected via a resistor R2 to a second signal path 6. Second signal path 6 is substantially identical to first signal path 4 but comprises a resistor R3 as a reference load instead of resonant circuit 5.

Both signal paths 4, 6 are fed to a measuring circuit 7, which determines the relative amplitude A of both signals as well as, optionally, their mutual phase shift phi. Relative amplitude A can e.g. be the amplitude of first signal path 4 in units of the amplitude of second signal path 6 (wherein the amplitudes are the peak values of the sine waves).

The output signal of measuring circuit 7 is fed to a microprocessor 8, which also controls the operation of VCO 1.

As can be seen from Fig. 1, the device in the present embodiment further comprises a temperature sensor 10, a display 11 and an input device 12 with user operable controls, all of which are controlled by microprocessor 8.

Inductance L of the device of Fig. 1 can be generated by a coil and/or by the leads and electrodes of capacitor C. Its value is generally known with reasonable accuracy.

Capacitor C of the device of Fig. 1 is used as an antenna for probing a specimen. For this purpose, it is formed by electrodes that are arranged near the specimen. The geometry of the electrodes is selected such that the electric field generated by them extends into the specimen and the body liquid to be measured. Suitable geometries are discussed below. As mentioned above, at least one of the electrodes of the capacitor is electrically isolated such that capacitor C is primarily a capacitive load, the capacitance and loss of which depends

on the electrical properties (i.e. the response) of the specimen at the frequency of VCO 1.

To measure the concentration of a substance in the body fluid of the specimen, microprocessor 8 can 5 e.g. initiate a measurement cycle consisting of a frequency sweep of VCO 1. The sweep should start at a frequency f_{min} below the expected resonance frequency f_0 of the resonant circuit 5 and extend to a frequency f_{max} above resonance frequency f . During this sweep, the electrical 10 properties of signal path 4 will change substantially, while those of signal path 6 will vary only slightly. The amplitude determined by measuring circuit A will therefore fall to a minimum A_0 at f_0 , as shown in Fig. 5. At the same time, phase shift ϕ crosses zero.

15 As can be shown, the dependence of A_0 on the dielectric constant $\epsilon(f)$ and, in particular, on the loss or conductance $\rho(f)$ of the fluid in the specimen is stronger than at off-resonance frequencies, which allows 20 a sensitive measurement of the liquid's response to the electric field.

This is shown in Fig. 8, which represents measurements of the type shown in Fig. 5 at glucose concentrations between 0 and 17.5 mmol/l. The vertical axis represents the ratio in dB of the signals from first 25 signal path 4 and second signal path 6. The resonance frequency is around 35.5 MHz.

It is presently believed that the specific impedance of the body fluid, i.e. the specific conductivity $\rho(f)$ and the dielectric constant $\epsilon(f)$ in a frequency 30 range between 10 MHz and 2000 MHz, and in particular between 20 MHz and 70 MHz, are a function of the properties and concentration of the salty (ionic) components of the human body. These salty components primarily include solvated sodium, potassium, calcium and other minor ions and 35 their counter ions, the primary counter ion being chloride. Other non-ionic solvated substances, in particular substances having a similar range of size as the ion com-

plexes, can have an impact on the impedance pattern of the salty body fluid components, provided these substances occur in sufficient concentration. In particular, glucose has a similar range of size and is present in 5 concentrations giving rise to a well detectable variation of the amplitude A0 at resonance frequency.

In a simple embodiment, only amplitude A0 is measured as a parameter for the determination of the concentration. Suitable calibration data stored in micro- 10 processor 8 is used to convert amplitude A0 into the desired concentration level.

The effects exploited for the measurement are temperature dependent. In order to obtain high accuracy over a wide temperature range, temperature sensor 10 is 15 brought into thermal contact with the specimen to be measured. The signals from temperature sensor 10 are used to correct the obtained result, again using calibration data obtain from calibration measurements.

A proper design of the electrodes of capacitor C allows to optimize the accuracy and sensitivity of 20 the present device in a given application. A preferred geometry of the device for in-vivo measurements in a living body is shown in Figs. 2 and 3.

The device comprises a housing 13 closed on 25 one side by an electrode plate 14. The display 11 is arranged opposite electrode plate 14. The electronic circuits 16 are arranged between electrode plate 14 and display 11.

Electrode plate 14 comprises an electrically 30 insulating substrate 17 with a strip electrode 18 and a top or ring electrode 19 arranged on an outer side 20 thereof. An inner side 21 of insulating substrate 17 is covered by a bottom electrode 22. A plurality of through- 35 contacts 23 are provided to connect ring electrode 19 to bottom electrode 22. A further through-contact 24 connects one end of strip electrode 18 to a small bond pad

25 arranged in an opening 26 of bottom electrode 22 on inner side 21.

Temperature sensor 10 is mounted to bottom electrode 22. The large number of through-contacts 23 ensure that bottom electrode 22 follows the temperature of ring electrode 18 and therefore the temperature of the specimen closely.

A typical size of electrode plate 14 is 32 mm x 21 mm. Bottom electrode 22 covers all of inner side 21 except for the small opening 26 and is therefore much larger than strip electrode 18.

Leads 28 are provided to connect bottom electrode 22, contact pad 26 and temperature sensor 10 to the electronic circuits 16.

While bottom electrode 22 and ring electrode 19 are connected to ground, strip electrode 18 is connected to inductance L of resonant circuit 5. Therefore, the capacitor C is formed between strip electrode 18 as a first electrode and ring electrode 19 and bottom electrode 22 as a second electrode. In other words, the second electrode consists of two electrode layers: a top electrode layer formed by ring electrode 19 and a bottom electrode layer formed by bottom electrode 22.

An electrically insulating cover layer 29 covers all of strip electrode 18 but not ring electrode 19. In other words, strip electrode 18 is arranged between substrate 17 and cover layer 29. Cover layer 29 is preferably of a hard, moisture- and salt-impervious material such as glass, ceramics, a polycarbonate or diamond-like carbon (DLC) of a thickness preferably between 50 and 100 μm .

As can be seen in Fig. 4, a holder or wristband 31 is attached to housing 13 for fixing the device to an arm or a leg of a human body with cover layer 29 facing the body and a longitudinal axis of strip electrode 18 parallel to the arm or leg. In this way, ring electrode 19 comes into contact with the user's skin and

sets the same to ground reference potential. The electric field generated by strip electrode 18 extends into the body tissue. Since strip electrode 18 is elongate and has a width much smaller than its length and extends along 5 the arm or leg, a comparatively large region of the body is reached by the field. This allows to obtain more sensitive and accurate measurements.

As described above, a pure sine voltage has been found to be sufficient for obtaining accurate measurements. However, other types for modulated voltages, 10 such as square-wave voltages or pulses can be used as well. In this case, measuring circuit 7 is preferably provided with suitable filters for selectively sampling one or more frequency components. At least one measured 15 frequency component is preferably close to the resonance frequency of resonant circuit 5 for exploiting the circuit's high sensitivity to the specimen's properties at that frequency.

The electrode geometry can be varied for 20 adapting it to a given application. While the design of Fig. 2 is optimized for a measurement on an arm or leg, a circular design can be used for measurement on a flatter body part or an in-vitro sample.

Ring electrode 19 does not necessarily have 25 to form a closed ring as long as it provides sufficient grounding of the body part to be measured. It can e.g. also have U-shape or consist of two stripes parallel to and laterally enclosing strip electrode 18. Ring electrode 19 can also be omitted completely or be covered by 30 cover layer 29, in particular for in-vitro measurements where noise is low.

Part of a further embodiment of the circuit is shown in Fig. 6. Here, no direct connection between resonant circuit 5 and measuring circuit 7 is used. 35 Rather, an antenna electrode 33 is located in proximity to the electrodes of capacitor C, and measuring circuit 7 measures the signal returned by antenna electrode 33.

A possible arrangement of the electrodes is shown in Fig. 7. As can be seen, antenna electrode 33 is strip shaped and arranged in parallel to strip electrode 18. Both, antenna electrode 33 and strip electrode 18 are 5 covered by cover layer 29 and therefore electrically insulated from the specimen.

The device of Figs. 6 and 7 is again sweeping VCO 1 between a frequency f_{min} below the resonance frequency f_0 of resonant circuit 5 and a frequency f_{max} 10 above it. In contrast to Fig. 5, measuring circuit 7 now detects a maximum amplitude A_0 at f_0 , wherein the value of A_0 depends on the response, i.e. the electrical properties of the specimen at the resonance frequency f_0 . The parameter A_0 can now again be processed using calibration 15 data as described above.

A comparison of the device of Figs. 1 and 2 with the device of Figs. 6 and 7 shows that the first embodiment measures the response of the specimen from the signal reflected to strip electrode 18. The second embodiment 20 measures the response of the specimen from the signal transmitted from strip electrode 18 to antenna electrode 33.

It is found that the transmission and reflection show different dependencies on the concentrations of 25 various compounds of the body fluid. Hence, a combined measurement of reflection and transmission allows a further refinement of the measurement by elimination of the influence of compounds not of interest for the quantity to be measured.

30 A third embodiment of a circuit is shown in Fig. 9. Here, the capacitor C formed by the electrodes is part of the resonant tank circuit of an active, self-oscillating oscillator 40. The amplitude A and frequency f_0 of the output signal of oscillator 40 depend on the 35 capacitance and losses in capacitor C. The corresponding signal is fed to measuring circuit 7, which evaluates the parameters A and f_0 . Measuring the corresponding parameters

ters A and f0 again allows a sensitive measurement of the desired concentration using calibration data.

In the examples shown so far, the invention was used in a device for qualitatively or quantitatively displaying the concentration a substance (such as glucose) in body liquid. The invention can, however, e.g. 5 also be used in devices that automatically administer medication to a body, such as an insulin pump, where the amount and/or time for administering the medication depends on the measured concentration. It can also be used 10 in any other type of device that requires the measurement of the concentration of a substance in body fluid.

While there are shown and described presently preferred embodiments of the invention, it is to be distinctly understood that the invention is not limited 15 thereto but may be otherwise variously embodied and practiced within the scope of the following claims.

Claims

1. A method for determining the concentration of a substance in a in-vitro or in-vivo specimen containing body liquid comprising the steps of
 - 5 arranging a first electrode (18) at said specimen, wherein said first electrode is electrically insulated from the specimen,
 - 10 applying a modulated electrical voltage to the first electrode for generating a modulated field in the specimen and
 - 15 measuring at least one parameter (A, phi) depending on a response of the specimen to the field and determining the concentration therefrom.
- 15 2. The method of claim 1 comprising the step of arranging a second electrode (19, 22) at said specimen, wherein the modulated electrical voltage is applied between the first and the second electrode (19, 22).
- 20 3. The method of claim 2 wherein the second electrode (19, 22) is in electric contact with the body liquid in the specimen.
- 25 4. The method of one of the preceding claims further comprising the step of measuring a temperature (T) of the specimen and using the temperature in the determination of the concentration.
5. The method of one of the preceding claims wherein the modulated electrical voltage is a sine voltage.
- 30 6. The method of one of the preceding claims wherein the modulated electrical voltage has a frequency between 10 MHz and 2 GHz, in particular between 20 MHz and 70 MHz.
- 35 7. The method of one of the preceding claims wherein the parameter (A, phi, f0) depends on the electrical impedance at the first electrode.

8. The method of one of the preceding claims wherein the response of the specimen is measured by measuring a signal reflected from the first electrode.

9. The method of one of the preceding claims 5 wherein an antenna electrode (33) is arranged at the specimen in proximity to the first electrode (18) and wherein the response of the specimen is measured by measuring a signal transmitted from the first electrode (18) to the antenna electrode (33).

10. The method of one of the preceding claims wherein the substance is glucose.

11. The method of one of the preceding claims wherein the specimen is a living body.

12. The method of one of the preceding claims 15 comprising the step of using calibration data to convert the parameter (A, phi, f0) to the concentration.

13. The method of one of the preceding claims wherein the first electrode forms part of a resonant circuit (5) having a resonance frequency (f0) and wherein 20 the resonant circuit (5) is operated substantially at the resonance frequency.

14. The method of claim 13 wherein the resonant circuit is at least part of a tank circuit of an active oscillator (40) and wherein the parameter is an amplitude (A) and/or a frequency (f0) of a signal generated by said oscillator (40).

15. The method of claim 13 wherein the modulated voltage is frequency sweeped from a frequency (fmin) below the resonance frequency (f0) to a frequency (fmax) above the resonance frequency, and in particular 30 wherein the parameter is a signal reflected to the first electrode (18) or transmitted to an antenna electrode (33) at the resonance frequency (f0).

16. A device for determining the concentration of a substance in a in-vitro or in-vivo specimen 35 containing body liquid, in particular for carrying out the method of one of the preceding claims, comprising

a first electrode (18) covered by a cover layer (29) of insulating material,

5 a signal source (1) connected to the first electrode (18) applying a modulated electrical voltage to the first electrode (18) for generating an electric field in the specimen,

10 a measuring circuit (7) for measuring at least one parameter depending on a response of the specimen to the field, and

15 a data processor (8) determining the concentration from the parameter.

17. The device of claim 16 comprising a holder (31) for fixing the first electrode (18) to a part of a body with the cover layer (29) facing the body.

18. The device of one of the claims 16 or 17 further comprising an electrically insulating substrate (17), wherein the first electrode (18) is arranged on a first side (20) of the substrate (17) between the substrate (17) and the cover layer (29).

20 19. The device of claim 18 further comprising a second electrode (19, 22) arranged on the substrate, wherein the signal source (2) is connected to apply the modulated electrical voltage between the first (18) and the second (19, 22) electrode.

25 20. The device of claim 19, wherein the second electrode (19, 22) comprises a bottom electrode layer (22) arranged on a second side (21) of the substrate (17), said bottom electrode layer (22) having a larger extension than said top electrode layer (18).

30 21. The device of one of the claims 19 or 20, wherein the second electrode (19, 22) comprises a top electrode layer (19) arranged on the first side (20) of the substrate (17), said top electrode layer (19) being arranged around at least part, in particular substantially all, of the first electrode (18).

22. The device of one of the claims 16 to 21, wherein the first electrode (18) is elongate having a width much smaller than a length.

23. The device of one of the claims 16 to 22 comprising a first (4) and a second (6) signal path between the signal source (1) and the measuring circuit (7), wherein the first electrode (18) is arranged in the first signal path (4) and a reference load (R3) is arranged in the second signal path (6), and wherein the measuring circuit (7) is adapted to measure a relative amplitude (A) and/or phase (phi) of signals from the first and second paths.

24. The device of one of the claims 16 to 23 wherein the first electrode (18) is part of a capacitor (C) of a resonant circuit (5) comprising the capacitor (C) and an inductance (L) connected to the signal source (1).

25. The device of claim 24 wherein the capacitor (C) and the inductance (L) are arranged in series.

26. The device of one of the claims 24 or 25 wherein the measuring circuit (7) is adapted to measure a voltage over the resonant circuit (5).

27. The device of one of the claims 24 to 26 further comprising an antenna electrode (33) arranged in proximity to the first electrode (18), wherein the measuring circuit (7) is adapted to measure a signal transmitted from the first electrode (18) to the antenna electrode (33).

28. A device for determining the concentration of a substance in body liquid of a human body, in particular of one of the claims 15 to 26, comprising an elongate first electrode (18) having a width much smaller than a length,

35 a holder (31) for fixing the first electrode (18) to an arm or leg of a body with a longitudinal axis

of the first electrode being substantially parallel to the arm or leg

5 a signal source connected to the first electrode applying a modulated electrical voltage to the first electrode (18) for generating a modulated field in the specimen,

a measuring circuit (7) for measuring at least one parameter (A, phi, f0) depending on a response of the specimen to the field, and

10 a data processor determining the concentration from the parameter.

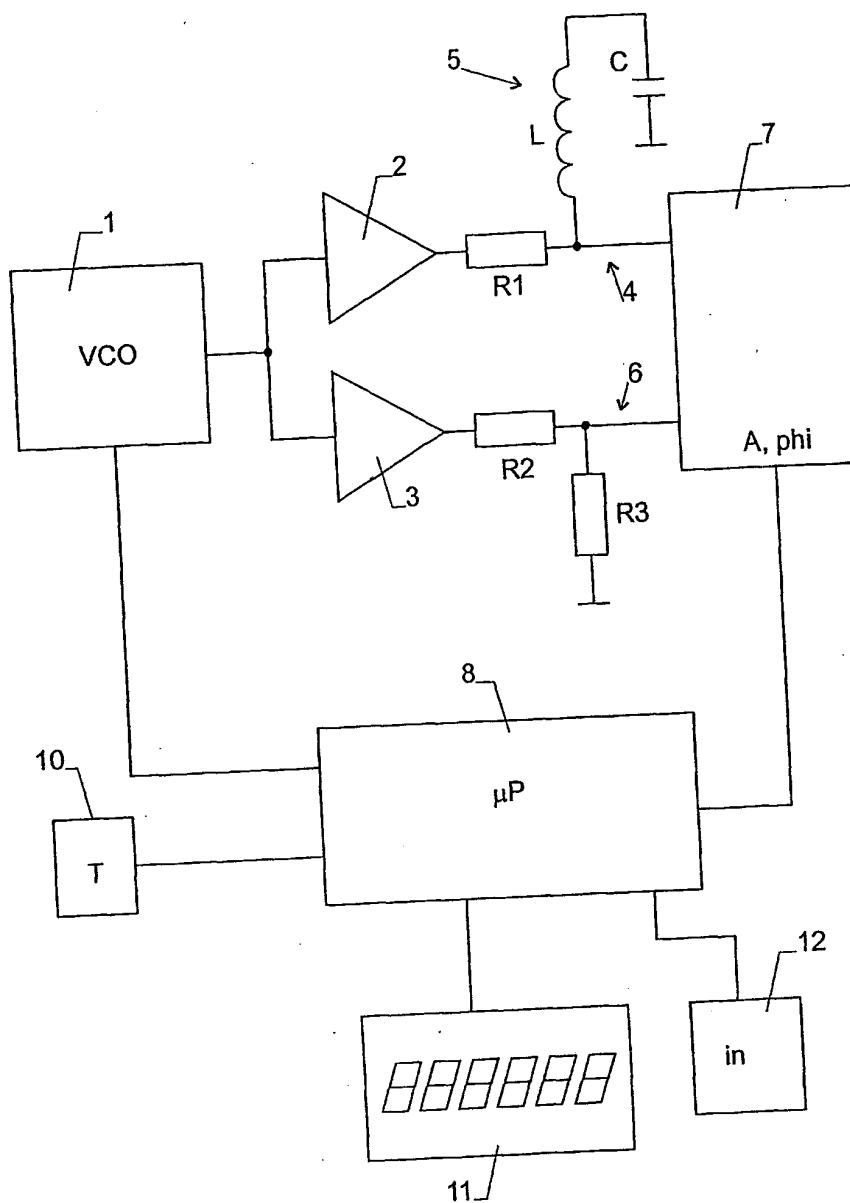


Fig. 1

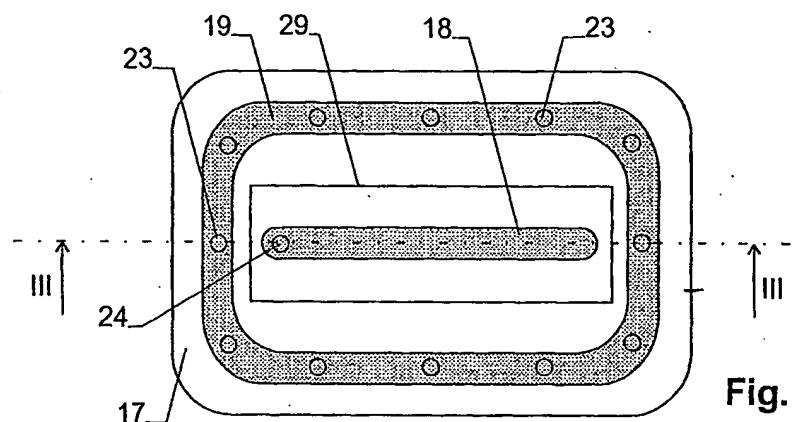


Fig. 2

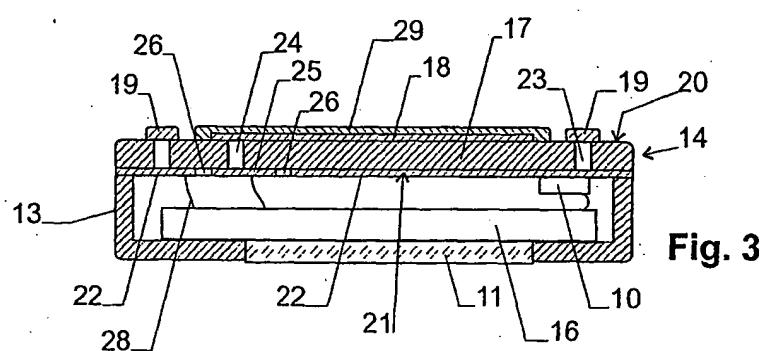


Fig. 3

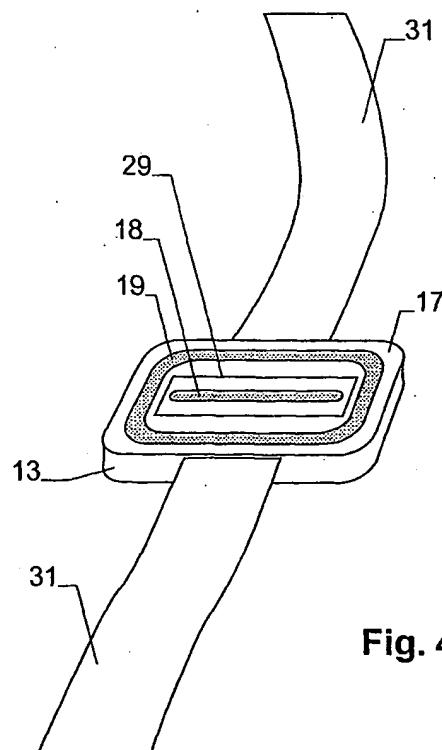


Fig. 4

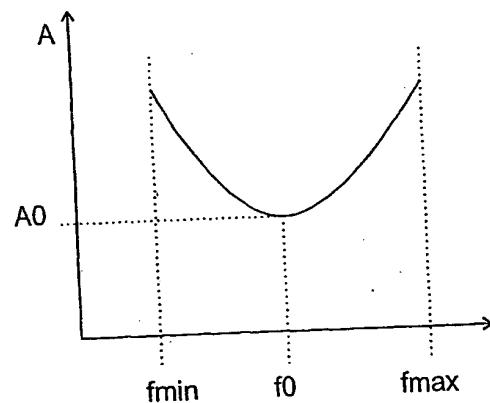


Fig. 5

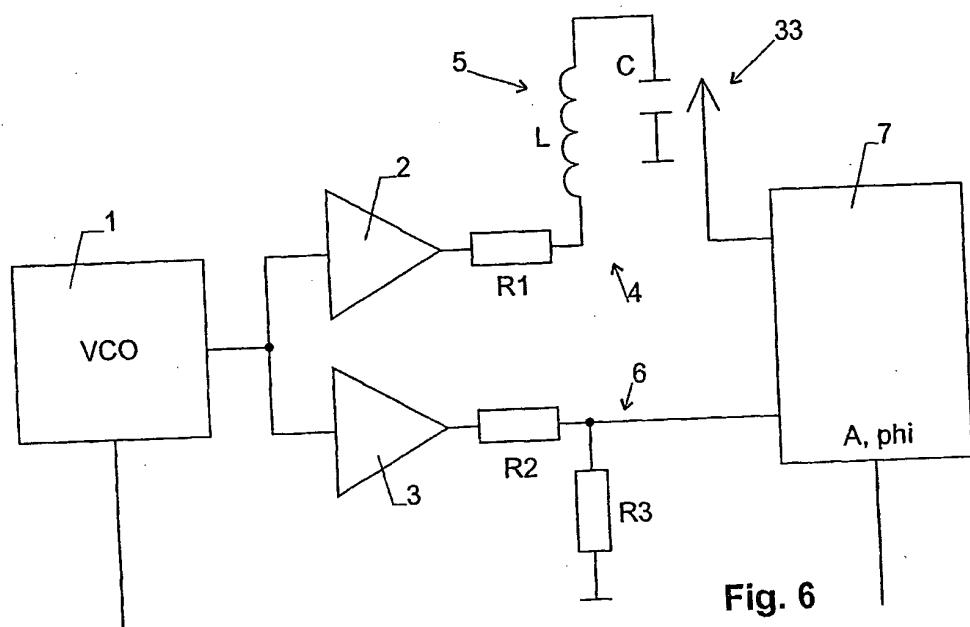


Fig. 6

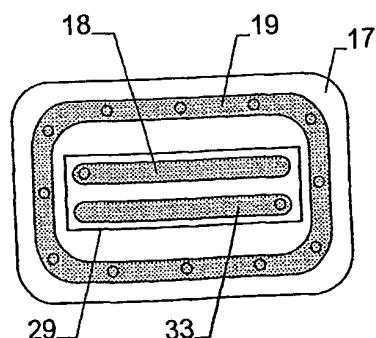


Fig. 7

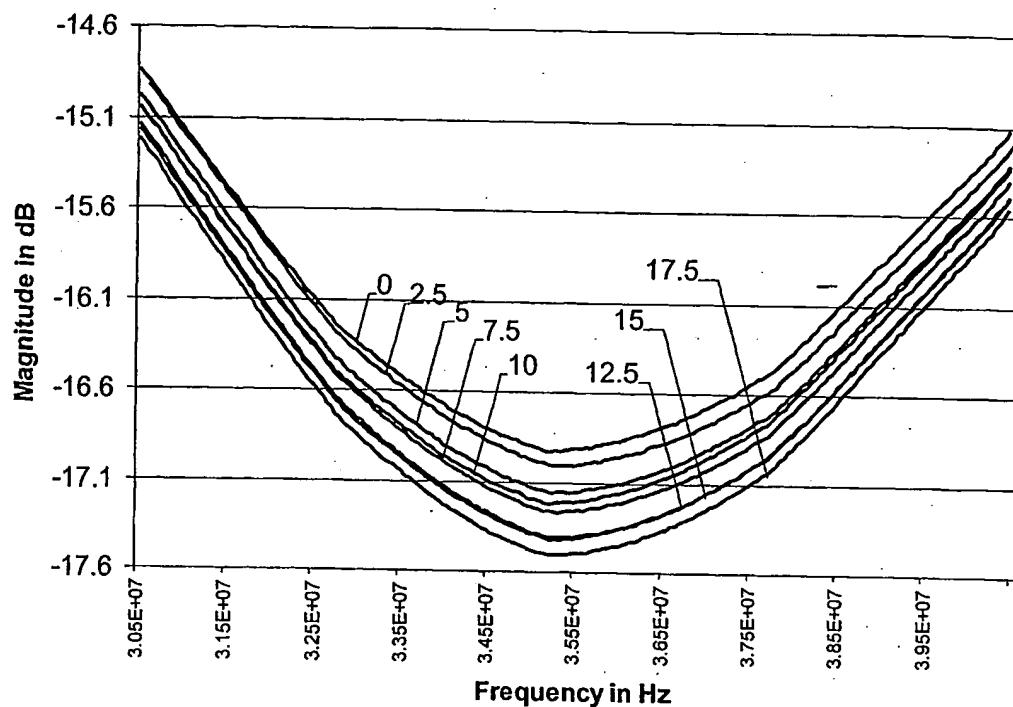


Fig. 8

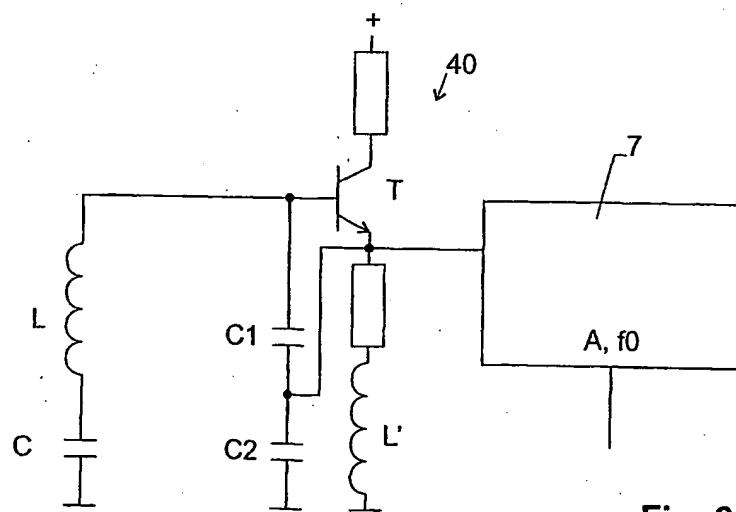


Fig. 9

INTERNATIONAL SEARCH REPORT

National Application No
PCT/IB 01/00334A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61B5/00 A61B5/05 G01N33/487 G01N22/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61B G01N

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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A	WO 00 43759 A (LUCAS JAMES ;UNIV LIVERPOOL (GB); AL SHAMMAA AHMED (GB)) 27 July 2000 (2000-07-27) page 5 page 18; figure 17	16
A	EP 0 298 441 A (MED & TECH HANDELS GMBH) 11 January 1989 (1989-01-11) abstract; figure 1	16
A	EP 0 309 085 A (FISHER SCIENTIFIC CO) 29 March 1989 (1989-03-29) abstract	16
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 Further documents are listed in the continuation of box C. Patent family members are listed in annex.

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Date of the actual completion of the international search

Date of mailing of the international search report

14 November 2001

21/11/2001

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Jonsson, P.O.

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tional Application No

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Information on patent family members

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